

## REMARKS

### *Status of the Claims*

With entry of this amendment, claims 1-35 and 46-65 are pending in the application. Claims 31-35 are withdrawn from consideration as being directed to a non-elected invention in accordance with the Restriction Requirement dated June 7, 2000. Claims 36-45 were previously canceled, without prejudice, in response to the Restriction Requirement. Claims 13-15, 17, 22-30, and 60-63 are withdrawn from consideration as directed to non-elected species. Rejoinder of these claims upon indication of allowable subject matter generic to these species is requested. Claims 1-12, 16, 18-21, 35, 46-59, and 54-65 are examined on the merits to the extent they read on the elected species. By this amendment, claim 1 has been amended in accordance with the Examiner's suggestions.

### *Specification*

The Examiner has objected to the amendment filed on November 25, 2002 is objected to under 35 U.S.C. 132 on the basis that it allegedly introduces new matter into the disclosure. The added material which the Examiner asserts is not supported by the original disclosure relates to the incorporation by reference of subject matter disclosed in priority documents 08/720,132 (now U.S. Patent 6,264,957) and 60/007,083. The Examiner notes that the applicant is permitted to claim priority to these documents for subject matter already disclosed in the present case, but asserts that it is not permitted to incorporate the entirety of these applications by reference on the basis that it would introduce material not previously incorporated in the application. Applicants respectfully traverse.

The instant application duly incorporated the disclosures of priority documents 08/720,132 and 60/007,083 (for example by express incorporation at page 149, lines 35-37, and page 175, lines 20-22, respectively) in the originally filed specification.

Applicants respectfully submit that this original incorporation obviates the stated new matter objection.

### ***Double Patenting***

Claims 1-12, 16, 18-21, 35, 46-59, and 64-65 are rejected for the reasons of record under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 96-103, 131, 151-153 of copending Application No. 09/444,067, and claims 20, 31, and 56 of copending application 09/444,221. Applicants note that this rejection is provisional, and will address the merits of the double patenting rejections upon allowance of one of the allegedly conflicting applications.

### ***Claim Rejections -35 USC § 112***

Claims 1-35, and 43-65 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that the original claims read on embodiments of RSV wherein the virus comprises any RNA polymerase elongation protein. The Examiner further states that “the specification, while being enabling for an isolated infectious chimeric RSV wherein the virus comprises the M2 (ORF1) RNA polymerase elongation factor, does not reasonably provide enablement for viruses containing any RNA polymerase elongation factor.”

Without addressing the merits of the subject rejection, Applicants note that the rejection is obviated by the amendment herein to claim 1 (and the respective dependent claims and claims reciting the recombinant RSV of claim 1). The subject claims now incorporate the clarifying language suggested by the Examiner—specifically reciting the “M2 (ORF1) RNA polymerase elongation factor” for which enabling support is recognized. Withdrawal of the rejection of claims 1-35, and 43-65 are rejected under 35 U.S.C. 112, first paragraph is therefore earnestly solicited.

***Patentability Under 35 USC § 103***

Applicants acknowledge that the Office has reconsidered and withdrawn the previous rejection of claims 1-12, 16, 18-21, 35, 46-59, 64, and 65 under 35 U.S.C. 103(a) as allegedly unpatentable over Murphy et al. in view of Collins et al. Accordingly, the Office's examination of the application now supports a finding that the application is free of the prior art.

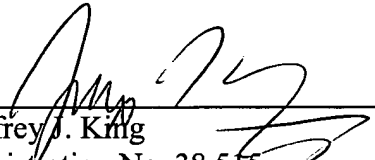
## CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (425) 455-5575.

Attached hereto is an appendix detailing the status of claims.

Date: 5/12/03

Respectfully submitted,

  
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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

1. (Currently and Previously Amended) An isolated infectious chimeric respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase protein (L), a M2 (ORF1) RNA polymerase elongation factor, and a partial or complete RSV genome or antigenome of one human RSV strain or subgroup virus combined with a heterologous gene or gene segment of a different human RSV strain or subgroup virus to form a chimeric RSV genome or antigenome.

2. (Previously Amended) The chimeric RSV of claim 1, wherein the chimeric genome or antigenome comprises a partial or complete human RSV genome or antigenome of one RSV subgroup or strain combined with a heterologous gene or gene segment from a different, human RSV subgroup.

3. (Previously Amended) The chimeric RSV of claim 2, wherein the heterologous gene or gene segment is from a human RSV subgroup A or human RSV subgroup B.

4. (Original) The chimeric RSV of claim 1, wherein the heterologous gene or gene segment is selected from a NS1, NS2, N, P, M, SH, M2(ORF1), M2(ORF2), L, F or G gene or gene segment.

5. (Original) The chimeric RSV of claim 4, wherein the heterologous gene or gene segment encodes a RSV F, G or SH glycoprotein or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof.

6. (Original) The chimeric RSV of claim 1, wherein the chimeric genome or antigenome comprises a partial or complete human RSV A subgroup genome or antigenome combined with a heterologous gene or gene segment from a human RSV B subgroup virus.

7. (Original) The chimeric RSV of claim 6, wherein the heterologous gene or gene segment from human RSV B encodes a RSV F, G or SH glycoprotein or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof.

8. (Original) The chimeric RSV of claim 6, wherein one or more human RSV B subgroup glycoprotein genes F, G and SH or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof is substituted within a RSV A genome or antigenome.

9. (Original) The chimeric RSV of claim 8, wherein one or both human RSV B subgroup glycoprotein genes F and G is substituted to replace one or both counterpart F and G glycoprotein genes in the RSV A genome or antigenome.

10. (Original) The chimeric RSV of claim 9, wherein both human RSV B subgroup glycoprotein genes F and G are substituted to replace the counterpart F and G glycoprotein genes in the RSV A genome or antigenome.

11. (Original) The chimeric RSV of claim 1, wherein a first heterologous gene or gene segment is substituted to replace a counterpart gene or gene segment within the partial or complete RSV genome or antigenome, and a second heterologous gene or gene segment is added to the partial or complete RSV genome or antigenome to form the chimeric RSV genome or antigenome.

12. (Original) The chimeric RSV of claim 1, wherein the chimeric genome or antigenome is further modified by one or more attenuating mutations.

13. (Original) The chimeric RSV of claim 12, wherein the chimeric genome or antigenome incorporates at least one and up to a full complement of attenuating mutations present within a panel of biologically derived mutant RSV strains, said panel

comprising *cpts* RSV 248 (ATCC VR 2450), *cpts* RSV 248/404 (ATCC VR 2454), *cpts* RSV 248/955 (ATCC VR 2453), *cpts* RSV 530 (ATCC VR 2452), *cpts* RSV 530/1009 (ATCC VR 2451), *cpts* RSV 530/1030 (ATCC VR 2455), RSV B-1 *cp*52/2B5 (ATCC VR 2542), and RSV B-1 *cp*-23 (ATCC VR 2579).

14. (Original) The chimeric RSV of claim 12, wherein the chimeric genome or antigenome incorporates at least one and up to a full complement of attenuating mutations specifying a temperature-sensitive amino acid substitution at Phe<sub>521</sub>, Gln<sub>831</sub>, Met<sub>1169</sub> or Tyr<sub>1321</sub> in the RSV polymerase gene L, or a temperature-sensitive nucleotide substitution in the gene-start sequence of gene M2.

15. (Original) The chimeric RSV of claim 12, wherein the chimeric genome or antigenome incorporates at least one and up to a full complement of mutations from cold-passaged attenuated RSV, said complement of mutations including mutations specifying an amino acid substitution at Val<sub>267</sub> in the RSV N gene, Glu<sub>218</sub> or Thr<sub>523</sub> in the RSV F gene, Cys<sub>319</sub> or His<sub>1690</sub> in the RSV polymerase gene L.

16. (Original) The chimeric RSV of claim 1, wherein each of the human RSV B subgroup glycoprotein genes F and G is added or substituted within a human RSV A genome or antigenome to form the chimeric genome or antigenome, which is further modified to incorporate one or more attenuating mutations.

17. (Original) The chimeric RSV of claim 16, wherein both human RSV B subgroup glycoprotein genes F and G are substituted to replace counterpart F and G glycoprotein genes within an RSV A genome or antigenome to form the chimeric genome or antigenome, which is further modified to incorporate attenuating point mutations selected from (i) a panel of mutations specifying temperature-sensitive amino acid substitutions at Gln<sub>831</sub> and Tyr<sub>1321</sub> in the RSV polymerase gene L; (ii) a temperature-sensitive nucleotide substitution in the gene-start sequence of gene M2; (iii) an attenuating panel of mutations adopted from cold-passaged RSV specifying amino acid

substitutions Val<sub>267</sub> Ile in the RSV N gene, and Cys<sub>319</sub> to Tyr and His<sub>1690</sub> Tyr in the RSV polymerase gene L; or (iv) a deletion of the SH gene.

18. (Original) The chimeric RSV of claim 12, wherein the chimeric genome or antigenome incorporates at least two attenuating mutations.

19. (Original) The chimeric RSV of claim 18, wherein the chimeric genome or antigenome incorporates attenuating mutations adopted from different biologically derived mutant RSV strains.

20. (Original) The chimeric RSV of claim 12, wherein the chimeric genome or antigenome includes at least one attenuating mutation stabilized by multiple nucleotide changes in a codon specifying the mutation.

21. (Original) The chimeric RSV of claim 1, formulated in a dose of  $10^3$  to  $10^6$  PFU of attenuated virus.

22. (Original) The chimeric RSV of claim 1 further comprising a nucleotide modification specifying a phenotypic change selected from a change in growth characteristics, attenuation, temperature-sensitivity, cold-adaptation, plaque size, host-range restriction, or a change in immunogenicity.

23. (Original) The chimeric RSV of claim 22, wherein a SH, NS1, NS2, M2ORF2, or G gene is modified.

24. (Original) The chimeric RSV of claim 23, wherein the SH, NS1, NS2, M2ORF2, or G gene is deleted in whole or in part or expression of the gene is ablated by introduction of one or more stop codons in an open reading frame of the gene.

25. (Original) The chimeric RSV of claim 22, wherein the nucleotide modification comprises a nucleotide deletion, insertion, substitution, addition or

rearrangement of a cis-acting regulatory sequence of a selected RSV gene within the chimeric RSV genome or antigenome.

26. (Original) The chimeric RSV of claim 25, wherein the cis-acting regulatory sequence of the selected RSV gene is changed to correspond to a heterologous regulatory sequence comprising a counterpart cis-acting regulatory sequence of the selected RSV gene from a different RSV subgroup or strain or a cis-acting regulatory sequence of a different RSV gene.

27. (Original) The chimeric RSV of claim 25, wherein a gene end (GE) signal of the NS1 or NS2 gene is modified to correspond to the GE signal of the RSV N gene.

28. (Original) The chimeric RSV of claim 22, wherein the nucleotide modification comprises an insertion, deletion, substitution, or rearrangement of a translational start site within the chimeric genome or antigenome.

29. (Original) The chimeric RSV of claim 28, wherein the translational start site for a secreted form of the RSV G glycoprotein is ablated.

30. (Original) The chimeric RSV of claim 22, wherein the chimeric genome or antigenome is modified to encode a non-RSV molecule selected from a cytokine, a T-helper epitope, a restriction site marker, or a protein of a microbial pathogen capable of eliciting a protective immune response in a mammalian host.

31. (Original) The chimeric RSV of claim 22, which incorporates a gene or gene segment from parainfluenza virus (PIV).

32. (Original) The chimeric RSV of claim 31, wherein the gene or gene segment encodes a PIV HN or F glycoprotein.

33. (Original) The chimeric RSV of claim 32, wherein the gene segment encodes a cytoplasmic tail, transmembrane domain, ectodomain or immunogenic epitope of HN or F of PIV1, PIV2, or PIV3.

34. (Original) The chimeric RSV of claim 1, wherein the chimeric genome or antigenome comprises a partial or complete human RSV genome or antigenome combined with an attenuating, heterologous gene or gene segment from a bovine or murine RSV.

35. (Previously Amended) The chimeric RSV of claim 1 which is a complete virus.

36. (Canceled) The chimeric RSV of claim 1 which is a subviral particle.

37. (Canceled) A method for stimulating the immune system of an individual to induce protection against RSV which comprises administering to the individual an immunologically sufficient amount of the chimeric RSV of claim 1 combined with a physiologically acceptable carrier.

38. (Canceled) The method of claim 37, wherein the chimeric RSV is administered in a dose of  $10^3$  to  $10^6$  PFU.

39. (Canceled) The method of claim 37, wherein the chimeric RSV is administered to the upper respiratory tract.

40. (Canceled) The method of claim 37, wherein the chimeric RSV is administered by spray, droplet or aerosol.

41. (Canceled) The method of claim 37, wherein the chimeric RSV is administered to an individual seronegative for antibodies to RSV or possessing transplacentally acquired maternal antibodies to RSV.

42. (Canceled) The method of claim 37, wherein the chimeric RSV is a chimera of human RSV A and RSV B which elicits an immune response against either human RSV A or RSV B.

43. (Canceled) The method of claim 37, wherein the chimeric RSV is a chimera of human RSV A and RSV B which elicits an immune response against both human RSV A and RSV B.

44. (Canceled) The method of claim 37, wherein the chimeric RSV is a chimera of human RSV A and RSV B which elicits an immune response against either human RSV A or RSV B and is co-administered with an immunologically sufficient amount of a second attenuated RSV capable of eliciting an immune response against human RSV A or RSV B, whereby an immune response is elicited against both human RSV A or RSV B.

45. (Canceled) The method of claim 44, wherein the chimeric RSV and second attenuated RSV are administered simultaneously as a mixture.

46. (Original) An immunogenic composition to elicit an immune response against RSV comprising an immunologically sufficient amount of the chimeric RSV of claim 1 in a physiologically acceptable carrier.

47. (Original) The immunogenic composition of claim 46, formulated in a dose of  $10^3$  to  $10^6$  PFU.

48. (Original) The immunogenic composition of claim 46, formulated for administration to the upper respiratory tract by spray, droplet or aerosol.

49. (Original) The immunogenic composition of claim 46, wherein the chimeric RSV is a chimera of human RSV A and RSV B which elicits an immune response against either human RSV A or RSV B.

50. (Original) The immunogenic composition of claim 46, wherein the chimeric RSV is a chimera of human RSV A and RSV B which elicits an immune response against both human RSV A and RSV B.

51. (Original) The immunogenic composition of claim 46, wherein the chimeric RSV is a chimera of human RSV A and RSV B which elicits an immune response against either human RSV A or RSV B and wherein the composition further comprises an immunologically sufficient amount of a second attenuated RSV capable of eliciting an immune response against human RSV A or RSV B, whereby the composition elicits an immune response against both human RSV A or RSV B.

52. (Previously Amended) An isolated polynucleotide molecule comprising a chimeric RSV genome or antigenome which includes a partial or complete human RSV genome or antigenome of one RSV strain or subgroup virus combined with a heterologous gene or gene segment of a different human RSV strain or subgroup virus.

53. (Previously Amended) The isolated polynucleotide molecule of claim 52, wherein the chimeric genome or antigenome comprises a partial or complete human RSV genome or antigenome of one RSV subgroup combined with a heterologous gene or gene segment from a different, human RSV subgroup.

54. (Previously Amended) The isolated polynucleotide molecule of claim 52, wherein the heterologous gene or gene segment is from a human RSV subgroup A or human RSV subgroup B.

55. (Original) The isolated polynucleotide molecule of claim 52, wherein the heterologous gene or gene segment encodes a RSV F, G or SH glycoprotein or a

cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof.

56. (Original) The isolated polynucleotide molecule of claim 52, wherein the chimeric genome or antigenome comprises a partial or complete human RSV A subgroup genome or antigenome combined with a heterologous gene or gene segment from a human RSV B subgroup virus.

57. (Original) The isolated polynucleotide molecule of claim 52, wherein one or both human RSV B subgroup glycoprotein genes F and G is substituted to replace one or both counterpart F and G glycoprotein genes in the RSV A genome or antigenome.

58. (Original) The isolated polynucleotide molecule of claim 57, wherein both human RSV B subgroup glycoprotein genes F and G are substituted to replace the counterpart F and G glycoprotein genes in the RSV A genome or antigenome.

59. (Original) The isolated polynucleotide molecule of claim 52, wherein the chimeric genome or antigenome is further modified by one or more attenuating mutations.

60. (Original) The isolated polynucleotide molecule of claim 52, wherein both human RSV B subgroup glycoprotein genes F and G are substituted to replace counterpart F and G glycoprotein genes within an RSV A genome or antigenome to form the chimeric genome or antigenome, which is further modified to incorporate attenuating point mutations selected from (i) a panel of mutations specifying temperature-sensitive amino acid substitutions Gln<sub>831</sub> to Leu and Tyr<sub>1321</sub> to Asn in the RSV polymerase gene L; (ii) a temperature-sensitive nucleotide substitution in the gene-start sequence of gene M2; (iii) an attenuating panel of mutations adopted from cold-passaged RSV specifying amino acid substitutions Val<sub>267</sub> Ile in the RSV N gene, and Cys<sub>319</sub> to Tyr and His<sub>1690</sub> Tyr in the RSV polymerase gene L; or (iv) a deletion of the SH gene.

61. (Original) The isolated polynucleotide molecule of claim 52, further comprising a nucleotide modification specifying a phenotypic change selected from a change in growth characteristics, attenuation, temperature-sensitivity, cold-adaptation, plaque size, host-range restriction, or a change in immunogenicity.

62. (Original) The isolated polynucleotide molecule of claim 61, wherein a SH, NS1, NS2, M2ORF2, or G gene is modified.

63. (Original) The isolated polynucleotide molecule of claim 61, wherein the nucleotide modification comprises a nucleotide deletion, insertion, addition or rearrangement of a cis-acting regulatory sequence of a selected RSV gene within the chimeric RSV genome or antigenome.

64. (Previously Amended) An expression vector for producing an infectious attenuated chimeric RSV comprising an isolated polynucleotide according to claim 52 operably linked with a transcriptional promoter and a transcriptional terminator.

65. (Previously Amended) A host cell for producing an infectious attenuated chimeric RSV comprising a mammalian cell susceptible to RSV infection transfected or transformed with an expression vector according to claim 64.